Charter for the Data and Safety Monitoring Boards of the Division of AIDS National Institute of Allergy and Infectious Diseases (09/28/09)

Overview

NIH policy requiring independent data and safety monitoring boards (DSMB) for all multicenter Phase III trials has existed since 1979; the most recent restatement was issued in 1998 (NIH Policy for Data and Safety Monitoring, NIH Guide Notice 98-084). In light of the related responsibility for monitoring assigned to local institutional review boards (IRB) by federal regulation (45 CFR 46), NIH added a requirement in 1999 that local IRBs be notified of the outcome of all DSMB reviews, even when no major change has been recommended, to document that data and safety monitoring is occurring as expected (Guidance on Reporting Adverse Events to Institutional Review Boards for NIH-Supported Multicenter Clinical Trials, NIH Guide Notice 99-107).

These NIH policies do not address implementation matters, leaving those to individual institutes and centers; various approaches are in use. As a result, the National Institute of Allergy and Infectious Diseases has issued its own policy on basic principles for DSMB operations (NIAID Policy on Data and Safety Monitoring Board (DSMB) Operations, V 3.0, Effective July 2, 2009. A copy of the NIAID Policy is provided in Attachment 2.

The Division of AIDS (DAIDS) monitors safety and efficacy of multicenter randomized clinical trials primarily through standing DSMBs. DAIDS believes that standing boards are both more effective and easier to manage than boards established separately for each new trial.

This document chiefly describes the organization and procedures of seven standing DSMBs that oversee most of the randomized trials carried out with funding from DAIDS. Currently these are the Therapeutics Trials DSMB formed in 1986, the Prevention Trials DSMB (formerly the Vaccine and Prevention DSMB created in 1998 by the merger of two DSMBs) and the HIV Vaccine DSMB formed in 2008, the International DSMBs – the Multinational DSMB formed in 2003, the African DSMB formed in 2005, the Asia DSMB formed in 2006, and the Zambia DSMB, a subgroup of the African DSMB formed in 2008. It is expected that other future DSMBs involved in oversight of DAIDS trials would have very similar characteristics, or at least conform to the basic principles articulated in the NIAID Policy. For trials involving collaboration between or among multiple research organizations there will usually need to be detailed discussions to arrive at trial-specific arrangements documented in a trial-specific charter.

Scope of Responsibilities

In general, DAIDS DSMB will review safety, efficacy, and overall study conduct as specified in the protocol for each trial. The Therapeutics Trials DSMB will oversee Phase III/IV trials conducted primarily in the US by the AIDS Clinical Trials Group (ACTG), the International Maternal Pediatric Adolescent AIDS Clinical Trials (IMPAACT), and any other network created in the future to conduct therapeutics research funded by DAIDS. Similarly, the Prevention Trials DSMB will oversee Phase II B and III/IV trials conducted by the HIV Prevention Trials Network (HPTN), the Microbicide Trials Network, and any other network created in the future to conduct prevention research funded by DAIDS. The HIV Vaccine DSMB will oversee Phase II B and III/IV trials conducted by the HIV Vaccine Trials Network (HVTN). The International DSMB – African and the International DSMB – Asia will oversee adult and pediatric therapeutics, vaccine, and prevention trials funded by DAIDS and conducted primarily in Africa and Asia, respectively. Trials are assigned by DAIDS to DSMBs according to the type of trial and geographic location of performance sites. The standing DSMBs are available to monitor Phase II, III and IV trials funded by DAIDS outside the networks (under investigator-initiated cooperative agreements, for instance).

There is no presumption that the DSMB will accept responsibility for monitoring any particular trial "as is" (i.e., as designed by the protocol team). It is necessary, therefore, to present each study to the

DSMB at the time of its initiation, preferably before enrollment begins. This initial review does not constitute participation in trial design, which would compromise the independence of the DSMB. Rather, it gives the DSMB an opportunity to communicate to DAIDS that it cannot take responsibility for oversight unless major issues and concerns are addressed. In this case, the DSMB will provide DAIDS a comprehensive list of specific issues that need to be resolved before assuming oversight responsibilities.

The DSMB's role does not necessarily end when the opportunity for stopping enrollment early passes. The DSMB should continue to review summaries of safety data by treatment group at least annually (local IRBs will be notified of the results of these reviews) until either safety follow-up ends or another entity assumes this responsibility.

The DSMB normally will have no role or responsibility for final analyses and preparation of manuscripts for publication.

Membership and Appointment Procedures

Membership of the DSMB should reflect the disciplines and medical specialties necessary to interpret the data from the trial, including medicine, statistics and potentially ethics. Selection of DSMB members should include consideration of clinical trials experience, relevant expertise, prior DSMB service and absence of significant conflict of interest. Terms of appointment are for four years and can be renewed. *Ad hoc* members may be added for reviews of specific studies to expand expertise or geographic representation as appropriate for the trial. To hold an official DSMB meeting a quorum consisting of at least three voting members must participate, including at least one clinician and one biostatistician.

No member of the DSMB should have any involvement in the conduct of the studies to be reviewed. Furthermore, no member should have certain financial, proprietary, professional, or other interests that may affect impartial, independent decision-making by the DSMB. Members may recuse themselves in the case of such potential conflicts. In general it is best to avoid appointing individuals who work in the same institution as the investigators. A lead investigator on one trial should not be a member of the DSMB for a different but similar trial. All regular and ad hoc DSMB members will sign a Conflict of Interest certification to that effect at the time they are asked to participate and periodically thereafter. Members will be asked to disclose any new interests that involve potential conflicts prior to each meeting; the DSMB will determine the appropriate means of dealing with any such disclosures for that meeting.

Input for the appointment of a new DSMB Chair is solicited from various sources including current Board members and NIAID staff. The Director of the Division of AIDS appoints the Chair.

Suggestions for potential Board members are similarly sought from various sources. In consultation with the appropriate Board Chair, network or study investigators, and NIAID staff, the NIAID Biostatistician, who acts as Executive Secretary, makes the final decision to appoint a Board member.

As indicated above, selection of members is more complicated when DAIDS networks collaborate with others. When the collaborator is another established research organization, appropriate representatives of each partner will develop plans jointly. For some studies, one of the existing DSMBs may not have representation from a country or region with a substantial number of participating clinical sites. In such cases, DAIDS policy is to add *ad hoc* members representing these countries or regions as necessary. These *ad hoc* members are identified in consultation with trial investigators, national ministries of health, and others.

Coordination of DSMB activities is the responsibility of a senior NIAID biostatistician, who acts as Executive Secretary. This individual oversees meeting planning and development of the meeting agendas, prepares the official meeting summaries and notifications of local IRBs, and serves as primary point of contact for inquiries regarding the DSMB.

Meeting Planning

The Therapeutics DSMB will meet approximately every six months for 1-2 days in Bethesda, MD. The HIV Vaccine DSMB will meet once a year for 1-2 days in Bethesda, MD. The Prevention Trials DSMB will meet every six months for 1-2 days in Bethesda, MD. The International DSMB – Africa and Zambia DSMB, the Multinational DSMB, and the Asia DSMB will meet approximately every six months for 1-2 days. The agenda for the meetings will be developed by the NIAID in conjunction with the statistical centers and the DSMB chair. In addition to studies scheduled for the required annual review, protocol initiation reviews and interim data reviews prompted by safety concerns or *a priori* protocol specifications are added to the schedule. A draft agenda as well as logistical information will be distributed to meeting participants (through the network headquarters where possible) two months in advance of the meeting. Two weeks prior to the meeting, NIAID will distribute the final agenda, copies of the protocols, summaries of previous DSMB reviews, as well as review assignments to the Board.

Meeting Conduct

Meetings will usually be face-to-face, occasionally by conference call (particularly for urgent reviews). Sessions will be of three types, not all of which would be needed at every meeting:

Open Session: This session is open to observers, including members of the protocol team, coordinating/data center staff, NIAID staff[*], representatives of industrial collaborators, or representatives from the Food and Drug Administration. This open session will deal with issues relating to the general conduct and progress of the study, such as accrual, patient demographics and other baseline characteristics, data quality control, adherence to the protocol, retention, and follow-up. Outcome results must not be discussed during this session. Discussion should be limited to the DSMB members, protocol chair, and statistician, and observers should refrain from participating unless asked a question or to volunteer a clarification.

Closed Session: At this session, safety and efficacy data by treatment group will be reviewed. Comparative results are presented to the DSMB in closed reports and closed sessions are normally attended only by voting members of the DSMB and one member of the NIAID staff or contractor serving as DSMB executive secretary (apart from the statistician who prepared the reports, who may in some instances be a NIAID employee or contractor, and a staff person to assist with taking notes). The study chair does not attend. Reports showing data by treatment group should mask the identity of the groups, and the DSMB will determine if and when to unmask.

To address an emerging safety issue, the designated DAIDS Medical Officer/Medical Monitor for the trial should provide a written request for access to closed safety reports (in a manner that minimizes unblinding) and attendance at the DSMB session dealing with safety analyses to the DAIDS Director for review and approval. The DAIDS Director is strongly encouraged to consult with the DSMB chair (through the NIAID Executive Secretary) before approving a request.

In other scenarios where DSMBs have documented significant deficiencies in closed data reports that impact their ability to perform an adequate review, a Division may need to provide support to the study statistician in order to maintain the integrity of the trial. Access to draft closed reports in these specific cases may be granted by the NIAID Deputy Director for Clinical Research and Special Projects to a qualified independent reviewer when needed to ensure quality of reports prior to DSMB submission. The independent reviewer will not perform any study safety monitoring functions, have any interactions with the study team, or be a member of the Program or Branch sponsoring the study. This reviewer may

[*] Some trials overseen by an NIAID DSMB are supported jointly by other NIH components and/or other federal agencies. In such cases, each supporting agency would be entitled to participate in meetings and receive reports under the same conditions as NIAID staff.

consult with a representative of the DSMB if needed to ensure that concerns of the Board are being fully addressed, but otherwise will have no interactions with the DSMB. Ideally, the Division should explore options of having the site contract directly with a qualified expert in lieu of an NIAID employee or contractor serving in this role. (In this scenario, a request for exception to policy would not be needed.) This type of exception should be requested only in critical situations where trial integrity could be compromised; future long term solutions need to be actively explored.

Closed Executive Session: This session involves only the DSMB members in order to ensure complete objectivity as they discuss outcome results, make decisions, and formulate recommendations regarding a study.

The DSMB will have the option to invite other participants to attend any part of the meeting to assist in fulfilling its responsibilities.

Study Reports

Meeting reports will be prepared by the study statistician(s) and distributed at least one and preferably two weeks prior to a scheduled meeting to those DSMB members and NIAID staff who will attend the meeting. The protocol team will determine contents and format initially; the DSMB may request additions and other modifications for subsequent reports.

Reports for the meetings consist of open and closed session reports. Open session reports are distributed to the protocol chair and to DSMB members and appropriate NIAID staff. Information in the open report includes data on study conduct, protocol compliance, site performance, quality control, follow-up, and baseline characteristics.

Closed reports are distributed only to DSMB members and the Executive Secretary. In addition to information included in the open report, the closed report includes safety and efficacy outcome data by treatment group. Closed session reports with safety data grouped by study arm will be made available to the designated DAIDS Medical Officer/Medical Monitor in circumstances when access to this safety data has been determined for a study. The designated DAIDS Medical Officer/Medical Monitor should provide a written request for access to closed safety reports (in a manner that minimizes unblinding) and attendance at the DSMB session dealing with safety analyses to the DAIDS Director for review and approval. The DAIDS Director is strongly encouraged to consult with the DSMB chair (through the NIAID Executive Secretary) before approving a request. Ordinarily the by-treatment reports are coded as a safeguard against disclosure through lost documents, and code keys are provided separately to members.

All material presented at any session will be considered confidential, and copies of reports for closed sessions, except for archival copies retained by the study statistician and the NIAID, will be collected and destroyed following the meeting. In general, closed reports are expected to be declassified not later than seven years after study completion.

DSMB Recommendations

Within two weeks of the meeting, the DSMB Executive Secretary works closely with the DSMB Chair to prepare a report summarizing the recommendations~~,~~ but none of the confidential information presented at the meeting. After approval of the summary recommendations by the full DSMB, the DSMB Executive Secretary submits the final version to the study chair and study statistician, to the director of the statistical center and the network chairs, as relevant, and to key DAIDS staff. The study chair is responsible for disseminating the DSMB summary report to other team members as necessary. In the case of trials conducted by networks, the network headquarters may take responsibility for distribution within the network (e.g., posting the meeting summary to a website and notifying investigators where to find it). In addition, it is acceptable for the DSMB to verbally share any recommendations of a routine nature with the team representatives and program officials immediately following the meeting.

In circumstances when there is a major recommendation (e.g., stop a study arm), the Board instead first communicates its formal recommendations only to the DSMB convening authority (NIAID leadership with rare exceptions). After consulting with the trial leadership and relevant staff, the DSMB convening authority's responsible official makes the final decision to accept the recommendations or not. If approved, the Executive Secretary circulates the DSMB recommendations as described above. Otherwise, a decision to reject a major recommendation will be communicated to the DSMB with appropriate rationale, after which the DSMB will reach a final determination on the recommendation and its distribution.

Reporting to IRBs

In fulfillment of the NIH Guidance on Reporting Adverse Events to Institutional Review Boards for NIH-Supported Multicenter Clinical Trials (release date: June 11, 1999), NIAID will distribute the final DSMB meeting summaries documenting the occurrence of the meeting and the recommendations to the Site investigators to forward to their Institutional Review Board (IRB)/Ethics Committee (EC).

Change History

The change summary table below will be updated when the document is reviewed or revised.

Version #	Date	Replaces	Date of Review/Revision	Rationale for Revision/ Retirement
3.0	07/14/09	V1.0	07/14/09	Clarification enhancements, newly formed DSMBs, clarification of procedures for access to closed safety data, new procedures for communicating final DSMB recommendations and definition of quorum established

Attachment 1

Standard Procedures to determine DAIDS MO Access to DSMB Closed Report Safety Analyses (09/28/09)

For new trials:

- For all DAIDS trials to be monitored by a DSMB, the assigned MO/MM will assess the study for level of risk and safety concerns during protocol development.
- All MO requests for access and the rationale will be discussed at the CSRC or PSRC review.
- The MO will also discuss whether to request access to the closed report safety data and the underlying safety concerns with his/her Branch Chief, who will forward a recommendation to the Director, Division of AIDS for final decision.
- Designated DAIDS Medical Officer/Medical Monitor should provide a written request for access to closed safety reports and attendance at the DSMB session dealing with safety analyses to their Division Director for review and approval. Division Directors are strongly encouraged to consult with the DSMB chair [through the NIAID Executive Secretary] before approving a request.
- The DSMB will be informed of decision and rationale to allow access to the closed session safety analyses at the protocol initiation review. The protocol statistician will be present and will be able to ensure that the study safety monitoring plan includes the proper reports for the MO to review.

For ongoing trials:

This general process will also be applied to trials currently reviewed by DSMBs. The request for access will be discussed at the Branch level and Program level before going forward. Discussion at the CSRC and PSRC is not required. Each DSMB will be informed of these requests for ongoing trials as soon as possible. Program will then provide the Statistical Centers with a list of ongoing studies that will have MO access to closed safety analyses.

For trials in which MO does not have access to closed session safety data:

If the MO does not have access to the closed session safety data for a DSMB-monitored study, the MO will receive interim reports with aggregated safety data as directed by the study safety monitoring plan. The MO may request access to closed report data, if any new information indicates a substantial safety concern. The DSMB and Statistical Center will be informed of the request as soon as possible.

Attachment 2

NIAID Policy on Data and Safety Monitoring Board (DSMB) Operations (PDF)